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THE WILLIAM ALLAN MEMORIAL AWARD

Presented to Yuet Wai Kan, M.D., F.R.S., at the annual meeting of the American Society of Human Genetics, Toronto, October 31–November 3, 1984

Introduction by

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It is with great pleasure that I announce that the recipient of the William Allan Memorial Award for 1984 is Yuet Wai (Y. W.) Kan. We honor Y. W. Kan, as he is known to the scientific community, as a pioneer in the application of molecular biology and genetics to clinical medicine. Kan has made a habit of being the first to answer a number of major questions in human molecular genetics. He was the first to demonstrate a gene deletion in man in α-thalassemia. He was the first to characterize a point mutation leading to β-thalassemia. In collaboration with Mitchell Golbus, he was the first to carry out prenatal diagnosis of a hemoglobinopathy. We honor him for these accomplishments, but our principal commendation is for his seminal observation of the clinical and practical importance of normal sequence variation in DNA: the *Hpa*I restriction site polymorphism adjacent to the β-globin gene and its clinically useful linkage disequilibrium with the sickle β-globin gene.

Kan was born 48 years ago in Hong Kong. (Note: I believe that it is still permissible to discuss the age of a *male* recipient of this award.) He received his medical degree along with the B.S. degree with honors from the University of Hong Kong in 1958 at age 22. At this point in his life, there was little sign of his future inclination toward research in molecular biology and genetics as he graduated with distinction in social medicine. That distinction, however, was a good indicator of his warmth and generosity.

Y. W. served as an intern and resident in medicine at Queen Mary Hospital, Hong Kong, and then came to this country in 1960 to be a fellow in hematology at the Peter Bent Brigham Hospital in Boston. During the first of several Boston experiences, he published a paper on polycythemia in hepatocellular carcinoma. In 1962–63, he became a resident in medicine at the University of

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Pittsburgh. He then had a series of short appointments: first as a research fellow for a year in biology at MIT, then as a research fellow for 2 years in hematology at McGill, and later as an associate in medicine for a year at University of Pennsylvania. Y. W. was training for the long haul, but it was in 1967 that he made the move which really shaped his career. He had been in post-residency training for about 5 years and had published just three papers, but at this point he went to the Boston Children's Hospital to train with David Nathan. Nathan was at that time in the process of setting up collaborations with top-notch members of the biology department at MIT, and a number of investigators in training, including Kan, benefitted from this arrangement. In 1967, Kan began to work on the thalassemias, measuring globin chain synthesis ratios in those early days and publishing papers on molecular biology of thalassemia with Nathan.

In 1970, he became an assistant professor at Harvard, and in the next 2 years, he began important work toward prenatal diagnosis of hemoglobinopathies through the measurement of β-globin chain synthesis in the fetus. In August 1971, I met Y. W. for the first time in the back of the auditorium at Woods Hole prior to an informal hemoglobin conference. I remember the meeting well because it was Bernie Forget, a mutual friend, who introduced us. Now Bernie was and still is a very bright guy who has himself done outstanding work in the hemoglobin gene story. I remember noting the tone in Bernie's voice when he introduced Kan. There was a sense of urgency and profound respect. I think Bernie was trying to tell me that I was meeting a "star." He was obviously right!

In 1972, Kan moved to San Francisco General Hospital as Chief of Hematology. He became a Howard Hughes Investigator in 1976, professor of medicine at UCSF in 1977, and professor of biochemistry and biophysics at UCSF in 1979. In 1983, he was named head of the Division of Genetics and Molecular Hematology of the Department of Medicine at UCSF in 1983 and the Louis K. Diamond Professor of Hematology.

Over the last 13 years, Y. W.'s productivity has been astounding. He has published over 120 papers, most in outstanding journals. As an interesting exercise, I studied his bibliography carefully and counted those papers which in my opinion had made a major impression on the globin gene field and molecular genetics in general. My conservative estimate was 35 such outstanding contributions! Prior to this award, Kan has already received a number of awards for his outstanding research, including the 1984 Gairdner Foundation Award and the 1984 Lita Annenberg Hazen Award for Excellence in Clinical Research. He has also given a number of named lectures, including the Harvey Lecture.

Because he has made so many important contributions to our genetic knowledge, I do not have time to mention them all, but I will mention those that are particularly striking. In 1974, Kan reported jointly with Bob Williamson's group the characterization of a gene deletion in man, the α-globin gene in α-thalassemia. Kan, with Golbus's help, carried out the first prenatal diagnoses for all the major hemoglobinopathies, α-thalassemia, β-thalassemia, and sickle-cell anemia in 1975 and 1976. In 1975, he reported another deletion, that of the

β-globin gene in hereditary persistence of fetal hemoglobin. In 1978, he showed that 30% of chromosomes bearing α-globin genes in blacks contain a single α gene, while the remaining 70% have two α-globin genes, the number commonly found in man. This polymorphism is still the most common one involving functional gene number known in man.

In the early summer of 1978, Kan, with Andrée Dozy, made his most important observation: a DNA polymorphism of an *Hpa*I restriction endonuclease site that was in linkage disequilibrium with the ^{S}-globin gene. Specifically, he found that the site was absent adjacent to the majority of β^S (sickle genes) but present next to nearly all normal β^A globin genes. He then immediately used this observation to carry out, in a clinical application, prenatal diagnosis of sickle-cell anemia by DNA analysis. The *Hpa*I polymorphism was not only the first DNA polymorphism observed in man, but it also had immediate clinical consequences. Now, in 1984, DNA polymorphisms are used in gene mapping, prenatal diagnosis, locating disease genes, haplotype analysis in the molecular characterization of genetic disease, and many other types of studies. The importance of Kan's observation cannot be overestimated.

In 1979, he discovered another DNA polymorphism which was useful in prenatal diagnosis of certain cases of β-thalassemia. In another landmark publication in 1980, Y. W. characterized the first point mutation in a β-thalassemia gene: a nonsense mutation. Also in 1980, Liebhaber and Kan published the nucleotide sequences of the two α-globin loci and their flanking DNA, which demonstrated the regions of sequence homology and gene correction events around these genes. More recently, Kan has published: (1) along with two other groups, the direct *Mst*II test for the sickle gene, (2) molecular characterization of a common Mediterranean β-thalassemia gene, (3) correction of a nonsense mutation in erythroid cells in vitro by introduction of a supressor tRNA gene, and (4) the usefulness of a new cosmid shuttle vector in gene cloning. This list of accomplishments merely gives examples of some of his first-class achievements; others, which may turn out in the long run to be even more worthy accomplishments, have been omitted.

Through all this productivity and hard work, Kan has managed to cultivate a wonderful family, including two children now in their late teens.

One last tribute to Y. W. is that he is highly respected by his colleagues and competitors as fair, intellectually honest, and scientifically critical. It is a great honor for me to present to you, Y. W. Kan, the William Allan Memorial awardee of 1984.